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[Intervention Protocol]

Pioglitazone for prevention or delay of type 2 diabetes mellitus and its associated complications in people at risk for the development of type 2 diabetes mellitus

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of pioglitazone for prevention or delay of type 2 diabetes mellitus and its associated complications in people at risk for the development of T2DM.

BACKGROUND

Description of the condition

'Prediabetes', 'borderline diabetes', the 'prediabetic stage', 'high risk of diabetes' or 'intermediate hyperglycaemia' (WHO/IDF 2006) are often characterised by various measurements of elevated blood glucose concentrations (such as isolated impaired fasting glucose (IFG), isolated impaired glucose tolerance (IGT), isolated elevated glycosylated haemoglobin A1c (HbA1c) or combinations thereof). These elevated blood glucose levels indicating hyperglycaemia are considered too high to be normal but below the diagnostic threshold for type 2 diabetes mellitus (T2DM). Therefore, because of the continuous spectrum from the normal to the diabetic stage, a sound evidence base is needed to define thresholds for conditions of 'sub-diabetes'. It is obvious that the different terms used to describe various stages of hyperglycaemia might induce different emotional reactions. For example, the term 'prediabetes' may imply (at least for the lay person) that diabetes is unavoidable whereas (high) risk of diabetes has the positive connotation that the disease may be avoided altogether. We will use all of the above-mentioned terms throughout this systematic review, however we will focus on 'prediabetes' because many people associate this label with dire consequences - despite the disputable construct of intermediate health states termed prediseases (Viera 2011). On the other hand, any diagnosis of 'prediabetes' might be an opportunity to review, for example, eating habits and physical activity levels, thus enabling affected individuals to actively change their way of life.

The most commonly used criteria to define people with a high risk of developing T2DM were established by the American Diabetes Association (ADA) and the World Health Organization (WHO). The first glycaemic measurement used to define the prediabetic stage by the US National Diabetes Data Group was IGT (NDDG 1979). IGT is based on the measurement of plasma glucose two hours after ingestion of 75 g glucose. The prediabetic range is defined as a plasma glucose level between 7.8 mmol/L to 11.1 mmol/L (140 mg/dL to 200 mg/dL) two hours after the glucose load. Studies have indicated that IGT is caused by insulin resistance and defective insulin secretion (Abdul-Ghani 2006). In 1997 the ADA and later on the WHO introduced the IFG concept to define 'prediabetes' (ADA 1997; WHO 1999). The initial definition of IFG was a fasting plasma glucose level of 6.1 mmol/L to 6.9 mmol/L (110 mg/dL to 125 mg/dL). Later on, the ADA reduced the lower threshold for defining IFG to 5.6 mmol/L (100 mg/dL) (ADA 2003). However, this lower cut-off point for IFG to define 'prediabetes' was not endorsed by the WHO (WHO/IDF 2006). IFG seems to be associated with β -cell dysfunction (impaired insulin secretion) and an increase of the hepatic glucose output (DeFronzo 1989). More recently, HbA1c has been introduced for identifying people with a high risk of developing T2DM. In 2009, the International Expert Committee (IEC) suggested the HbA1c to identify people with a high risk of T2DM. People with HbA1c measurements between 6.0% to 6.4% fulfilled this criterion (IEC 2009). Shortly after, the ADA redefined this HbA1c level as 5.7% to 6.4% to identify people with a high risk of developing T2DM (ADA 2010). Unlike IFG and IGT, HbA1c reflects longer-term glycaemic control, that is, how the blood glucose levels have been during the previous two to three months (Inzucchi 2012).

In 2010, the International Diabetes Federation (IDF) estimated the prevalence of IGT to be 343 million, and this number is predicted to increase to 471 million by 2035 (IDF 2013). Studies have shown

poor correlations between HbA1c and IFG/IGT (Gosmanov 2014; Selvin 2011). Moreover, the various glycaemic tests do not seem to identify the same people (Gosmanov 2014; Selvin 2011). The risk of progression from 'prediabetes' to T2DM depends on the diagnostic criteria used to identify 'prediabetes' (Richter 2018). Some people diagnosed with 'prediabetes' will never develop T2DM, and some will return to normoglycaemia (Richter 2018). IFG and HbA1c are both thought to predict a different risk spectrum for developing T2DM (Cheng 2006; Morris 2013). Most importantly, dysglycaemia is commonly an asymptomatic condition, and naturally often remains 'undiagnosed' (CDC 2015).

Currently, ADA recommends reduced calorie intake and increased physical activity for people with increased risk of T2DM (ADA 2017). It is still not clarified if any particular intervention, especially glucose-lowering drugs, should be recommended for people with 'prediabetes' (Yudkin 2014). Studies have indicated that the progression from 'prediabetes' to T2DM is reduced, or maybe just delayed with 'lifestyle' interventions (usually increased physical activity, dietary changes or both) (Diabetes Prevention Program 2002; Diabetes Prevention Program FU 2009; Finnish Diabetes Prevention Study Group 2001). A recent meta-analysis of 22 studies with behaviour-changing interventions in people at high risk of T2DM concluded that the effect of behaviour-changing interventions on longer-term diabetes prevention had not been clarified (Dunkley 2014).

The prescription of pharmacological glucose-lowering interventions for the prevention of T2DM is not generally accepted among international diabetes associations and clinicians. Several groups of pharmacological glucose-lowering interventions have been investigated in people with 'prediabetes'. Some findings indicate that the progression from 'prediabetes' to T2DM is reduced or maybe just delayed (Diabetes Prevention Program 2002; Diabetes Prevention Program FU 2009). However, the ADA recommends metformin for people with 'prediabetes' and a body mass index (BMI) more than 35 kg/m², aged less than 60 years, and for women with prior gestational diabetes mellitus (ADA 2015). Several Cochrane Reviews have not shown prevention of T2DM after use of various antidiabetic medications (Hemmingsen 2016a; Hemmingsen 2016b; Hemmingsen 2017).

Description of the intervention

Oral antidiabetic agents are most often used to treat T2DM in its initial stages if behaviour changing modifications have failed. Pioglitazone affects many tissues and parts of the body. For people with T2DM, pioglitazone can be prescribed as monotherapy or in combination with existing glucose-lowering interventions (Davies 2019). Currently, pioglitazone is not recommended for people with intermediate hyperglycaemia. The cost of pioglitazone is low in most countries (Davies 2019).

Pioglitazone is a member of the thiazolidinedione group which also encompasses troglitazone (withdrawn due to hepatic toxicity) and rosiglitazone (withdrawn from several markets due to suspected cardiovascular risk) (Babai 2018; Cohen 2010).

Adverse effects of the intervention

The most common adverse effects of pioglitazone are heart failure, bone fracture, oedema and weight gain (Liao 2017; Richter 2006).

How the intervention might work

Pioglitazone is known to improve insulin sensitivity, glycaemic control, hypertension and dyslipidaemia in people with T2DM (Scherthaner 2013). Pioglitazone decreases fasting and postprandial plasma glucose levels by improving the sensitivity of hepatic and peripheral (muscle) tissue to insulin (Scherthaner 2013). By improving insulin sensitivity, thiazolidinediones may exert beneficial effects on cardiovascular risk factors (Scherthaner 2013).

Pioglitazone exerts its action through a selective and potent inhibition of peroxisome proliferator-activated receptor (PPAR)-gamma (Ninomiya 2016). PPARs are transcription factors that reside in the nucleus and become activated by ligands such as thiazolidinediones. Thiazolidinediones enter the cell, bind to the nuclear receptors, and alter the expression of genes. There are several PPARs including PPAR-alpha, PPAR-beta/delta, and PPAR-gamma. PPAR-gamma receptors are present in adipose, hepatic and skeletal muscle tissue and control insulin-responsive genes, which have a wide-ranging influence (Ninomiya 2016).

Why it is important to do this review

There has been an increased focus on the prevention or delay of T2DM with non-pharmacological interventions and glucose-lowering medications. Currently, several studies are being conducted to clarify whether the progression from an at-risk status to T2DM can be stopped or postponed with glucose-lowering agents (ClinicalTrials.gov). However, a more important issue for people with dysglycaemia is whether the intervention reduces the risk of death or complications - especially cardiovascular disease - related to T2DM.

One systematic review evaluated the effects of pioglitazone in people with T2DM, insulin resistance and intermediate hyperglycaemia. However, the investigators did not search for unpublished data nor applied rigorous Cochrane methodology (Liao 2017). This review concluded that pioglitazone was associated with a reduced risk of macrovascular complications (all types of participants combined). However, the risks of heart failure, bone fracture, oedema and weight gain were increased (Liao 2017).

OBJECTIVES

To assess the effects of pioglitazone for prevention or delay of type 2 diabetes mellitus and its associated complications in people at risk for the development of T2DM.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs).

Types of participants

Nondiabetic individuals at risk of developing T2DM, i.e. diagnosed with intermediate hyperglycaemia or 'prediabetes'.

Diagnostic criteria for 'prediabetes'

To be consistent with changes in the classification of and diagnostic criteria for 'prediabetes' (IFG, IGT and elevated HbA1c) over the

years, the diagnosis should have been established using the standard criteria valid at the time of the study commencing (for example ADA 1997; ADA 2010; NDDG 1979; WHO 1999). Ideally, the diagnostic criteria should be described. If necessary, we will use the study authors' definition of 'prediabetes'. Differences of glycaemic measurements used to define 'prediabetes' may introduce substantial heterogeneity. We therefore plan to subject diagnostic criteria to a subgroup analysis.

Types of interventions

We plan to investigate the following comparisons of intervention versus control/comparator intervention.

Intervention

- Pioglitazone as monotherapy.
- Pioglitazone as a part of a dual combination therapy.

Comparisons

- Any pharmacological glucose-lowering monotherapy intervention (e.g. acarbose, metformin, sulphonylurea) compared with pioglitazone as monotherapy.
- Behaviour-changing interventions (e.g. diet, exercise, diet and exercise) compared with pioglitazone as monotherapy.
- Placebo compared with pioglitazone as monotherapy.
- No intervention compared with pioglitazone as monotherapy.
- Any pharmacological glucose-lowering agent (e.g. acarbose, metformin, sulphonylurea) compared with pioglitazone as a part of a dual combination therapy. This glucose-lowering agent has to be identical in both the intervention and comparator groups (e.g. pioglitazone plus metformin versus metformin or pioglitazone plus acarbose versus acarbose plus metformin).

Other concomitant interventions (e.g. educational programmes or additional pharmacotherapy) have to be identical in both the intervention and comparator groups to establish fair comparisons.

If a study includes multiple arms, we will include any arm that meets the review inclusion criteria.

Minimum duration of intervention

We will include studies with a duration of the intervention of 24 weeks or more to establish effects on patient-relevant outcomes.

Minimum duration of follow-up

The minimum duration of follow-up should be 24 weeks (end of the intervention period).

We will define any follow-up period going beyond the original time frame for the primary outcome measure as specified in the power calculation of the study's protocol as an extended follow-up period (also called 'open-label extension study') (Buch 2011; Megan 2012).

Summary of specific exclusion criteria

- We will exclude studies of people exclusively diagnosed with the 'metabolic syndrome' because this is a special population which is not representative of people with only intermediate hyperglycaemia. Also, the composite of risk indicators such as elevated blood lipids, insulin resistance, obesity and hypertension, which is termed 'metabolic syndrome' is of

doubtful clinical usefulness and uncertain distinct disease entity.

- We will exclude studies evaluating participants with intermediate hyperglycaemia in combination with another condition (e.g. cystic fibrosis).
- We will exclude studies evaluating participants with intermediate hyperglycaemia because of other medical interventions (e.g. glucocorticoids).

We will include studies in obese people and participants with previous gestational diabetes, if study investigators describe that the participants have intermediate hyperglycaemia. We will include a study even if it does not report one or more of our primary or secondary outcome measures in the publication. If a study does not report any of our primary or secondary outcomes, we will include this study and contact the corresponding study author for supplementary data.

Types of outcome measures

We will investigate the following outcomes using the methods and time points specified below.

Primary outcomes

- All-cause mortality.
- Incidence of T2DM.
- Serious adverse events.

Secondary outcomes

- Cardiovascular mortality.
- Non-fatal myocardial infarction.
- Non-fatal stroke.
- Amputation of lower extremity.
- Blindness or severe vision loss.
- End-stage renal disease.
- Non-serious adverse events.
- Hypoglycaemia.
- Health-related quality of life.
- Time to progression to T2DM.
- Measures of blood glucose control.
- Socioeconomic effects.

Method of outcome measurement

- All-cause mortality: defined as death from any cause.
- Incidence of T2DM and time to progression to T2DM: defined according to diagnostic criteria valid at the time the diagnosis was established, using the standard criteria valid at the time of the study commencing (e.g. [ADA 2008](#); [WHO 1998](#)). If necessary, we will use the study authors' definition of T2DM.
- Serious adverse events: defined according to the International Conference on Harmonization Guidelines as any event that led to death, that was life-threatening, required in-patient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability, and any important medical event that may have had jeopardised the participant or required intervention to prevent it ([ICH 1997](#)), or as reported in studies.

- Cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, amputation of lower extremity, blindness or severe vision loss, hypoglycaemia (mild, moderate, severe/serious): defined as reported in studies.
- End-stage renal disease: defined as dialysis, renal transplantation or death due to renal disease.
- Non-serious adverse events: defined as number of participants with any untoward medical occurrence not necessarily having a causal relationship with the intervention.
- Health-related quality of life: defined as mental and physical health-related quality of life, separate and combined, evaluated by a validated instrument such as Short-Form 36 (SF-36).
- Measures of blood glucose control: fasting blood glucose, blood glucose two hours after ingestion of 75 g glucose and HbA1c measurements.
- Socioeconomic effects: for example costs of the intervention, absence from work, medication consumption.

Timing of outcome measurement

- Measured at the end of the intervention and the end of follow-up: all-cause mortality, cardiovascular mortality, blindness or severe vision loss, end-stage renal disease, health-related quality of life, measures of blood glucose control, socioeconomic effects.
- Measured at the end of the intervention and the longest reported end of follow-up: incidence of T2DM.
- Measured at any time of the intervention and during follow-up: serious adverse events, non-serious adverse events, hypoglycaemia (mild, moderate, severe/serious),

Search methods for identification of studies

Electronic searches

We will search the following sources from the inception of each database to the date of search and will place no restrictions on the language of publication:

- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO);
- MEDLINE (Ovid MEDLINE ALL 1946 to Daily Update);
- ClinicalTrials.gov (www.clinicaltrials.gov);
- World Health Organization International Clinical Trials Registry Platform (ICTRP) (www.who.int/trialsearch/).

For detailed search strategies, see [Appendix 1](#).

We will not include Embase in our search, as RCTs indexed in Embase are now prospectively added to CENTRAL via a highly sensitive screening process ([Cochrane 2018](#)).

Searching other resources

We will try to identify other potentially eligible studies or ancillary publications by searching the reference lists of included studies, systematic reviews, meta-analyses, and health technology assessment reports. In addition, we will contact the authors of included studies to obtain additional information on the retrieved studies and establish whether we may have missed further studies.

We will also search databases from regulatory agencies (European Medicines Agency (EMA) and US Food and Drugs Administration (FDA)) ([Hart 2012](#); [Schroll 2015](#)).

We will not use abstracts or conference proceedings for data extraction unless full data are available from study authors because this information source does not fulfil the CONSORT requirements which consists of quote: "an evidence-based, minimum set of recommendations for reporting randomized trials" ([CONSORT 2018](#)). We will present information on abstracts or conference proceedings in the 'Characteristics of studies awaiting classification' table. We define grey literature as records detected in [ClinicalTrials.gov](#), WHO ICTRP or databases from regulatory agencies.

Data collection and analysis

Selection of studies

Two review authors (BR, BH) will independently screen the abstract, title, or both, of every record retrieved by the literature searches, to determine which studies we should assess further. We will obtain the full text of all potentially relevant records. We will resolve disagreements through consensus or by recourse to a third review author (KM). If we cannot resolve a disagreement, we will categorise the study as a 'Study awaiting classification' and will contact the study authors for clarification. We will present an adapted PRISMA flow diagram to show the process of study selection ([Liberati 2009](#)). We will list all articles excluded after full-text assessment in a 'Characteristics of excluded studies' table and will provide the reasons for exclusion.

Data extraction and management

For studies that fulfil our inclusion criteria, two review authors (EI and KM or BH) will independently extract key participant and intervention characteristics. We will describe interventions according to the 'template for intervention description and replication' (TIDieR) checklist ([Hoffmann 2014](#); [Hoffmann 2017](#)).

We will report data on efficacy outcomes and adverse events using standardised data extraction sheets from the CMED Group. We will resolve disagreements by discussion or, if required, by consultation with a third review author (BR).

We will provide information including trial identifier for potentially relevant ongoing trials in the 'Characteristics of ongoing trials' table and in a joint appendix 'Matrix of study endpoint (publications and trial documents)'. We will try to find the protocol for each included study and will report in a joint appendix primary, secondary, and other outcomes in comparison with data in publications.

We will email all authors of included studies to enquire whether they would be willing to answer questions regarding their studies. We will present the results of this survey in an appendix. We will thereafter seek relevant missing information on the study from the primary study author(s), if required.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents, or multiple reports of a primary study, we will maximise the information yield by collating all available data, and we will use the most complete data set aggregated across all known publications. We will list duplicate publications, companion documents, multiple

reports of a primary study, and trial documents of included trials (such as trial registry information) as secondary references under the study ID of the included study. Furthermore, we will list duplicate publications, companion documents, multiple reports of a study, and trial documents of excluded trials (such as trial registry information) as secondary references under the study ID of the excluded study.

Data from clinical trials registers

If data from included trials are available as study results in clinical trials registers, such as [ClinicalTrials.gov](#) or similar sources, we will make full use of this information and extract the data. If there is also a full publication of the study, we will collate and critically appraise all available data. If an included study is marked as a completed study in a clinical trial register but no additional information (study results, publication, or both) is available, we will add this study to the 'Characteristics of studies awaiting classification' table.

Assessment of risk of bias in included studies

Two review authors (EI and KM or BH) will independently assess the risk of bias for each included study. We will resolve disagreements by consensus or by consulting a third review author (BR). In the case of disagreement, we will consult the remainder of the review author team and make a judgment based on consensus. If adequate information is unavailable from the publications, study protocols, or other sources, we will contact the study authors for more detail to request missing data on 'Risk of bias' items.

We will use the Cochrane 'Risk of bias' assessment tool ([Higgins 2017](#)), assigning assessments of low, high, or unclear risk of bias (for details, see [Appendix 2](#); [Appendix 3](#)). We will evaluate individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions*, according to the criteria and associated categorisations contained therein ([Higgins 2017](#)).

Summary assessment of risk of bias

We will present a 'Risk of bias' graph and a 'Risk of bias' summary figure.

We will distinguish between self-reported, investigator-assessed and adjudicated outcome measures.

We will consider the following self-reported outcomes.

- Non-serious adverse events.
- Hypoglycaemia, if reported by participants.
- Health-related quality of life.
- Blood glucose control, if measured by study participants.

We will consider the following outcomes to be investigator-assessed.

- All-cause mortality.
- Incidence of T2DM.
- Time to progression to T2DM.
- Serious adverse events.
- Cardiovascular mortality.
- Non-fatal myocardial infarction.
- Non-fatal stroke.
- Amputation of lower extremity.

- Blindness or severe vision loss.
- End-stage renal disease.
- Hypoglycaemia, if measured by study personnel.
- Blood glucose control, if measured by study personnel.
- Socioeconomic effects.

Risk of bias for a study across outcomes

Some Risk of bias' domains, such as selection bias (sequence generation and allocation sequence concealment), affect the risk of bias across all outcome measures in a study. In case of high risk of selection bias, we will mark all endpoints investigated in the associated study as being at high risk. Otherwise, we will not perform a summary assessment of the risk of bias across all outcomes for a study.

Risk of bias for an outcome within a study and across domains

We will assess the risk of bias for an outcome measure by including all entries relevant to that outcome (i.e. both study-level entries and outcome-specific entries). We consider low risk of bias to denote a low risk of bias for all key domains, unclear risk to denote an unclear risk of bias for one or more key domains and high risk to denote a high risk of bias for one or more key domains.

Risk of bias for an outcome across studies and across domains

These are the main summary assessments that we will incorporate into our judgments about the certainty of the evidence in the 'Summary of findings' table(s). We will define outcomes as at low risk of bias when most information comes from studies at low risk of bias, unclear risk when most information comes from studies at low or unclear risk of bias and high risk when a sufficient proportion of information comes from studies at high risk of bias.

Measures of treatment effect

When at least two included studies are available for a comparison of a given outcome, we will try to express dichotomous data as a risk ratio (RR) or an odds ratio (OR) with 95% confidence intervals (CIs). For continuous outcomes measured on the same scale (e.g. weight loss in kg) we will estimate the intervention effect using the mean difference (MD) with 95% CIs. For continuous outcomes that measure the same underlying concept (e.g. health-related quality of life) but use different measurement scales, we will calculate the standardised mean difference (SMD). We will express time-to-event data as a hazard ratio (HR) with 95% CIs.

Unit of analysis issues

We will take into account the level at which randomisation occurred, such as cross-over studies, cluster-randomised trials, and multiple observations for the same outcome. If more than one comparison from the same study is eligible for inclusion in the same meta-analysis, we will either combine groups to create a single pairwise comparison, or we will appropriately reduce the sample size so that the same participants do not contribute data to the meta-analysis more than once (splitting the 'shared' group into two or more groups). Although the latter approach offers some solution for adjusting the precision of the comparison, it does not account for correlation arising from inclusion of the same set of participants in multiple comparisons (Higgins 2011b).

We will attempt to re-analyse cluster-RCTs that have not appropriately adjusted for potential clustering of participants

within clusters in their analyses. Variance of the intervention effects will be inflated by a design effect. Calculation of a design effect involves estimation of an intracluster correlation coefficient (ICC). We will obtain estimates of ICCs by contacting study authors, or by imputing ICC values using either estimates from other included studies that report ICCs or external estimates from empirical research (e.g. Bell 2013). We plan to examine the impact of clustering by performing sensitivity analyses.

Dealing with missing data

If possible, we will obtain missing data from the authors of included studies. We will carefully evaluate important numerical data such as screened, randomly assigned participants, as well as intention-to-treat and as-treated and per-protocol populations. We will investigate attrition rates (e.g. dropouts, losses to follow-up, withdrawals), and we will critically appraise issues concerning missing data and use of imputation methods (e.g. last observation carried forward).

For studies in which the standard deviation (SD) of the outcome is not available at follow-up or we cannot re-created it, we will standardise by the mean of the pooled follow-up SD from studies that reported this information.

When included studies do not report means and SDs for outcomes, and we do not receive requested information from study authors, we will impute these values by estimating the mean and the variance from the median, the range and the size of the sample (Hozo 2005).

We will investigate the impact of imputation on meta-analyses by performing sensitivity analyses, and we will report for every outcome which studies had imputed SDs.

Assessment of heterogeneity

In the event of substantial clinical or methodological heterogeneity, we will not report study results as the pooled effect estimate in a meta-analysis.

We will identify heterogeneity (inconsistency) by visually inspecting the forest plots and by using a standard χ^2 test with a significance level of $\alpha = 0.1$ (Deeks 2017). In view of the low power of this test, we will also consider the I^2 statistic, which quantifies inconsistency across studies, to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003).

When we find heterogeneity, we will attempt to determine possible reasons for this by examining individual study and subgroup characteristics.

Assessment of reporting biases

If we include 10 or more studies that investigated a particular outcome, we will use funnel plots to assess small-study effects. Several explanations may account for funnel plot asymmetry, including true heterogeneity of effect with respect to study size, poor methodological design (and hence bias of small studies), and publication bias (Sterne 2017). Therefore we will interpret the results carefully (Sterne 2011).

Data synthesis

We plan to undertake (or display) a meta-analysis only if we judge participants, interventions, comparisons, and outcomes to be

sufficiently similar to ensure an answer that is clinically meaningful. Unless good evidence shows homogeneous effects across studies of different methodological quality, we will primarily summarise low risk of bias data using a random-effects model (Wood 2008). We will interpret random-effects meta-analyses with due consideration for the whole distribution of effects and will present a prediction interval (Borenstein 2017a; Borenstein 2017b; Higgins 2009). A prediction interval requires at least three studies to be calculated and specifies a predicted range for the true treatment effect in an individual study (Riley 2011). For rare events such as event rates below 1%, we will use the Peto odds ratio method, provided there is no substantial imbalance between intervention and comparator group sizes, and intervention effects are not exceptionally large. In addition, we will perform statistical analyses according to the statistical guidelines presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017).

Subgroup analysis and investigation of heterogeneity

We expect the following characteristics to introduce clinical heterogeneity, and we plan to carry out the following subgroup analyses including investigation of interactions (Altman 2003).

- Studies with a long duration (four years and longer) versus studies with a shorter duration (less than four years).
- Diagnostic 'prediabetes' criteria (IFG, IGT, elevated HbA1c).
- Pioglitazone monotherapy versus pioglitazone dual combination therapy.
- Age, depending on data.
- Sex.
- Ethnicity, depending on data.
- Comorbid conditions, such as hypertension or obesity.
- Women with and without previous gestational diabetes mellitus.

Sensitivity analysis

We plan to perform sensitivity analyses to explore the influence of the following factors (when applicable) on effect sizes by restricting analysis to the following.

- Published studies.
- Effect of risk of bias, as specified in the [Assessment of risk of bias in included studies](#) section.
- Very long or large studies to establish the extent to which they dominate the results.
- Use of the following filters: diagnostic criteria, imputation, language of publication, source of funding (industry versus other) or country.

We will test the robustness of results by repeating analyses using different measures of effect size (i.e. RR, OR, etc.) and different statistical models (fixed-effect and random-effects models).

Certainty of the evidence

We will present the overall certainty of the evidence for each outcome specified below, according to the GRADE approach, which

takes into account issues related not only to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity, such as directness of results. Two review authors (BH, BR) will independently rate the certainty of the evidence for each outcome. We will resolve differences in assessment by discussion or by consultation with a third review author (KM).

We will include an appendix entitled 'Checklist to aid consistency and reproducibility of GRADE assessments', to help with standardisation of the 'Summary of findings' tables (Meader 2014). Alternatively, we will use the GRADEpro Guideline Development Tool (GDT) software and will present evidence profile tables as an appendix (GRADEproGDT 2015). We will present results for outcomes as described in the [Types of outcome measures](#) section. If meta-analysis is not possible, we will present the results in a narrative format in the 'Summary of findings' table. We will justify all decisions to downgrade the certainty of the evidence by using footnotes, and we will make comments to aid the reader's understanding of the Cochrane Review when necessary.

'Summary of findings' table

We will present a summary of the evidence in a 'Summary of findings' table. This will provide key information about the best estimate of the magnitude of effect, in relative terms and as absolute differences for each relevant comparison of alternative management strategies, numbers of participants and studies addressing each important outcome, and a rating of overall confidence in effect estimates for each outcome. We will create the 'Summary of findings' table using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017), along with Review Manager (RevMan 5.3) table editor (RevMan 2014). We plan to present in the 'Summary of findings' table the interventions pioglitazone as monotherapy or as part of a dual combination therapy and the comparator interventions behaviour-changing interventions, placebo, no intervention or any pharmacological glucose-lowering agent as a part of a dual combination therapy.

We will report the following outcomes, listed according to priority.

- All-cause mortality.
- Incidence of T2DM.
- Serious adverse events.
- Cardiovascular mortality.
- Non-fatal myocardial infarction/stroke.
- Health-related quality of life.
- Socioeconomic effects.

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APPENDICES

Appendix 1. Search strategies

MEDLINE (Ovid SP)

1. Prediabetic state/
2. Glucose Intolerance/
3. (prediabet* or pre diabet*).tw.
4. (intermediate hyperglyc?emi*).tw.

(Continued)

5. ((impaired fasting adj2 glucose) or IFG or impaired FPG).tw.
6. glucose intoleran*.tw.
7. ((impaired glucose adj (tolerance or metabolism)) or IGT).tw.
8. ((risk or progress* or prevent* or inciden* or conversion or develop* or delay*) adj4 (diabetes or T2D* or NIDDM or "type 2" or "type II")).tw.
9. or/1-8
10. Pioglitazone/
11. (pioglitazon* or "U 72107A" or "U72,107A" or "U72107A" or "AD 4833" or "AD4833").tw.
12. 10 or 11
13. 9 and 12
- [Cochrane Handbook RCT filter - sensitivity max. version + [Cooper 2019](#) "phase3 filter"]
14. randomized controlled trial.pt.
15. controlled clinical trial.pt.
16. randomi?ed.ab.
17. placebo.ab.
18. drug therapy.fs.
19. randomly.ab.
20. trial.ab.
21. groups.ab.
22. or/14-21
23. exp animals/ not humans/
24. 22 not 23
25. Clinical Trial, Phase III/
26. ("phase 3" or "phase3" or p3 or "pIII").ti,ab,kw.
27. 25 or 26
28. 24 or 27
- 13 and 28

Cochrane Central Register of Controlled Trials (Cochrane Register of Studies Online)

1. MESH DESCRIPTOR Prediabetic state
2. MESH DESCRIPTOR Glucose Intolerance
3. (prediabet* OR pre diabet*):TI,AB,KY
4. (intermediate hyperglyc?emi*):TI,AB,KY
5. ((impaired fasting ADJ3 glucose) OR IFG OR impaired FPG):TI,AB,KY
6. glucose intoleran*:TI,AB,KY

(Continued)

7. ((impaired glucose ADJ2 (tolerance OR metabolism)) OR IGT):TI,AB,KY
8. ((risk OR progress* OR prevent* OR inciden* OR conversion OR develop* OR delay*) ADJ5 (diabetes OR T2D* OR NIDDM OR "type 2" OR "type II")):TI,AB,KY
9. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10. MESH DESCRIPTOR Pioglitazone
11. (pioglitazon* OR "U 72107A" OR "U72,107A" OR "U72107A" OR "AD 4833" OR "AD4833"):TI,AB,KY
12. #10 OR #11
13. #9 AND #12

WHO ICTRP (Standard search)

prediabet* AND pioglitazone OR
pre-diabet* AND pioglitazone OR
impaired* AND glucose* AND pioglitazone OR
impaired* AND fasting* AND pioglitazone OR
glucose* AND intoleran* AND pioglitazone OR
IFG* AND pioglitazone OR
IGT* AND pioglitazone

ClinicalTrials.gov (Expert search)

(prediabetes OR prediabetic OR "pre diabetes" OR "pre diabetic" OR "impaired glucose" OR "impaired fasting" OR "glucose intolerance" OR IGT OR IFG OR ((diabetes OR "type 2" OR "type II" OR T2D OR T2DM) AND (risk OR progress OR progression OR progressed OR incident OR incidence OR conversion OR developed OR development OR develop OR delay OR delayed OR prevention OR prevent OR prevented))) [DISEASE] AND pioglitazone [TREATMENT]

Appendix 2. 'Risk of bias' assessment

'Risk of bias' domains

Random sequence generation (selection bias due to inadequate generation of a randomised sequence)

For each included study, we will describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

- Low risk of bias: study authors achieved sequence generation using computer-generated random numbers or a random numbers table. Drawing of lots, tossing a coin, shuffling cards or envelopes, and throwing dice are adequate if an independent person performed this who was not otherwise involved in the study. We will consider the use of the minimisation technique as equivalent to being random.
- Unclear risk of bias: insufficient information about the sequence generation process.
- High risk of bias: the sequence generation method was non-random or quasi-random (e.g. sequence generated by odd or even date of birth; sequence generated by some rule based on date (or day) of admission; sequence generated by some rule based on hospital or clinic record number; allocation by judgment of the clinician; allocation by preference of the participant; allocation based on the results of a laboratory test or a series of tests; or allocation by availability of the intervention).

Allocation concealment (selection bias due to inadequate concealment of allocation prior to assignment)

(Continued)

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and we will assess whether intervention allocation could have been foreseen in advance of or during recruitment or changed after assignment.

- Low risk of bias: central allocation (including telephone, interactive voice-recorder, internet-based and pharmacy-controlled randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.
- Unclear risk of bias: insufficient information about the allocation concealment.
- High risk of bias: used an open random allocation schedule (e.g. a list of random numbers); assignment envelopes used without appropriate safeguards; alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

We will also evaluate study baseline data to incorporate assessment of baseline imbalance into the 'Risk of bias' judgement for selection bias ([Corbett 2014](#)).

Chance imbalances may also affect judgements on the risk of attrition bias. In the case of unadjusted analyses, we will distinguish between studies that we rate as being at low risk of bias on the basis of both randomisation methods and baseline similarity, and studies that we judge as being at low risk of bias on the basis of baseline similarity alone ([Corbett 2014](#)). We will reclassify judgements of unclear, low, or high risk of selection bias as specified in [Appendix 3](#).

Blinding of participants and study personnel (performance bias due to knowledge of the allocated interventions by participants and personnel during the study)

We will evaluate the risk of detection bias separately for each outcome ([Hróbjartsson 2013](#)). We will note whether endpoints were self-reported, investigator-assessed, or adjudicated outcome measures (see below).

- Low risk of bias: blinding of participants and key study personnel was ensured, and it was unlikely that the blinding could have been broken; no blinding or incomplete blinding, but we judge that the outcome is unlikely to have been influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of participants and study personnel; the study does not address this outcome.
- High risk of bias: no blinding or incomplete blinding, and the outcome is likely to have been influenced by lack of blinding; blinding of study participants and key personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.

Blinding of outcome assessment (detection bias due to knowledge of the allocated interventions by outcome assessment)

We will evaluate the risk of detection bias separately for each outcome ([Hróbjartsson 2013](#)). We will note whether endpoints were self-reported, investigator-assessed, or adjudicated outcome measures (see below).

- Low risk of bias: blinding of outcome assessment is ensured, and it is unlikely that the blinding could have been broken; no blinding of outcome assessment, but we judge that the outcome measurement is unlikely to have been influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of outcome assessors; the study did not address this outcome.
- High risk of bias: no blinding of outcome assessment, and the outcome measurement was likely to have been influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data (attrition bias due to quantity, nature or handling of incomplete outcome data)

For each included study or each outcome, or both, we will describe the completeness of data, including attrition and exclusions from the analyses. We will state whether the study reported attrition and exclusions, and we will report the number of participants included in the analysis at each stage (compared with the number of randomised participants per intervention/comparator groups). We will also note if the study reported the reasons for attrition or exclusion, and whether missing data were balanced across groups or were related to outcomes. We will consider the implications of missing outcome data per outcome such as high dropout rates (e.g. above 15%) or disparate attrition rates (e.g. difference of 10% or more between study arms).

- Low risk of bias: no missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to introduce bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (mean difference or standardised mean difference) among missing outcomes was not enough to have a clinically relevant impact on observed effect size; appropriate methods, such as multiple imputation, were used to handle missing data.
- Unclear risk of bias: insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias; the study did not address this outcome.
- High risk of bias: reason for missing outcome data was likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared

(Continued)

with observed event risk enough to induce clinically relevant bias in the intervention effect estimate; for continuous outcome data, plausible effect size (mean difference or standardised mean difference) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' or similar analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.

Selective reporting (reporting bias due to selective outcome reporting)

We will assess outcome reporting bias by integrating the results of the appendix 'Matrix of study endpoints (publications and trial documents)' (Boutron 2014; Jones 2015; Mathieu 2009), with those of the appendix 'High risk of outcome reporting bias according to the Outcome Reporting Bias In Trials (ORBIT) classification' (Kirkham 2010). This analysis will form the basis for the judgement of selective reporting.

- Low risk of bias: the study protocol was available and all the study's prespecified (primary and secondary) outcomes that were of interest to this review were reported in the prespecified way; the study protocol was unavailable, but it was clear that the published reports included all expected outcomes (ORBIT classification).
- Unclear risk of bias: insufficient information about selective reporting.
- High risk of bias: not all the study's prespecified primary outcomes were reported; one or more primary outcomes were reported using measurements, analysis methods, or subsets of the data (e.g. subscales) that were not prespecified; one or more reported primary outcomes were not prespecified (unless clear justification for their reporting was provided, such as an unexpected adverse effect); one or more outcomes of interest in the Cochrane Review were reported incompletely so that we cannot enter them into a meta-analysis; the study report failed to include results for a key outcome that we would expect to have been reported for such a study (ORBIT classification).

Other bias

- Low risk of bias: the study appears to be free from other sources of bias.
- Unclear risk of bias: information was insufficient to assess whether an important risk of bias existed; insufficient rationale or evidence that an identified problem introduced bias.
- High risk of bias: the study had a potential source of bias related to the specific study design used; the study was claimed to be fraudulent; or the study had some other serious problem.

Appendix 3. Selection bias decisions

Selection bias decisions for studies that reported unadjusted analyses: comparison of results obtained using method details alone versus results obtained using method details and study baseline information^a

Reported randomisation and allocation concealment methods	'Risk of bias' judgement using methods reporting	Information gained from study characteristics data	'Risk of bias' using baseline information and methods reporting
Unclear methods	Unclear risk	Baseline imbalances present for important prognostic variable(s)	High risk
		Groups appear similar at baseline for all important prognostic variables	Low risk
		Limited or no baseline details	Unclear risk
Would generate a truly random sample, with robust allocation concealment	Low risk	Baseline imbalances present for important prognostic variable(s)	Unclear risk^b
		Groups appear similar at baseline for all important prognostic variables	Low risk

(Continued)

		Limited baseline details, showing balance in some important prognostic variables ^c	Low risk
		No baseline details	Unclear risk
Sequence is not truly randomised or allocation concealment is inadequate	High risk	Baseline imbalances present for important prognostic variable(s)	High risk
		Groups appear similar at baseline for all important prognostic variables	Low risk
		Limited baseline details, showing balance in some important prognostic variables ^c	Unclear risk
		No baseline details	High risk

^aTaken from [Corbett 2014](#); judgements highlighted in bold indicate situations in which the addition of baseline assessments would change the judgement about risk of selection bias compared with using methods reporting alone.

^bImbalance was identified that appears likely to be due to chance.

^cDetails for the remaining important prognostic variables are not reported.

CONTRIBUTIONS OF AUTHORS

All review authors contributed to, read and approved the final protocol draft.

DECLARATIONS OF INTEREST

Emil Ørskov Ipsen (EI): had an inadvertent conflict of interest because he had owned a small number of shares with Novo Nordisk A/S before registering the title. Without prompting EI amended the situation by selling the shares June 11th 2019. The Cochrane Metabolic and Endocrine Disorders contacted the Cochrane Funding Arbiter for guidance, who agreed to allow the review to proceed with EI as a first author, providing that this issue was clearly explained in the declarations of interest.

Kasper Madsen (KM): none known.

Ulrik Pedersen-Bjerggaard: has served on advisory panels for Novo Nordisk and Sanofi Aventis and received an unrestricted research grant from Novo Nordisk.

Bernd Richter (BR): none known.

Maria-Inti Metzendorf (MIM): none known.

Bianca Hemmingsen (BH): none known.

NOTES

We have based parts of the [Methods](#), as well as [Appendix 1](#), [Appendix 2](#), and [Appendix 3](#) of this Cochrane Protocol, on a standard template established by the CMED Group.